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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,274	01/12/2001	John Sinden	GJE-21D2	3086

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 05/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/760,274	Applicant(s) SINDEN ET AL.	
	Examiner Michael Wilson	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *1-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 & 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Election/Restriction

Applicant's election of Groups V, claims 49-56, in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Claims 49-56 are under consideration in the instant office action.

Specification

The first line of the specification needs updated.

Priority

This application repeats a substantial portion of prior Application No. 09/672606, filed 9-28-00, and adds and claims additional disclosure not presented in the prior application (see claims 52-59 and new matter rejection below). Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application and not a continuation as claimed. The priority document cannot be found in 09/672606.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 52-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed in the parent application does not provide support for claims 52-56. In particular, the specification does not teach transplanting nestin-positive cells as claimed. Therefore, claims 52-56 are new matter. Applicants are requested to point to support by page and line number.

2. Claims 49-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for implanting rat hippocampal neuroepithelial cells in the hippocampus of a rat having a damaged hippocampus, does not reasonably provide enablement for using any cell as broadly claimed for treatment, treating any behavioral or psychological deficit in any animal, or using cells comprising exogenous DNA for treatment as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The state of the art at the time of filing was such that it is unpredictable how to target particular areas of the brain when transplanting neural cells (Scheffler et al., 1999, Trends in

Neuroscience, Vol. 22, pages 348-357; see paragraph bridging pages 354 and 355). The specification teaches obtaining the pluripotent neuroepithelial CA1 cells from the hippocampus, transplanting the cells to the CA1 area of rats with damaged CA1 tissue of the hippocampus and obtaining an improved performance as compared to control animals in the water maze test (page 22). The specification does not teach the cells migrate or teach implanting the cells into a different area of the brain and obtaining a therapeutic effect. Therefore, the specification does not enable administering cells into a damaged brain (claim 49) or by intracerebral transplantation (claim 52) as broadly claimed.

The water maze test used by applicants is an assay for determining spacial learning and memory in an animal. Sinden (1997, Neuroscience, Vol. 81, pages 599-608) teach that for transplanted neural cells to restore performance in water maze tests, the cells must be CA1 cells derived from the hippocampus and highly specific to the damaged CA1 tissue (page 601, paragraph bridging columns 1 and 2). For example, CA1 cells are effective, but CA3 cells derived from the hippocampus or cells derived from other portions of the brain are not effective (page 601, sentence bridging columns 1 and 2). The specification does not provide any guidance indicating pluripotent neuroepithelial cells obtained from CA3 cells or from any other brain tissue can be used to treat damage any behavioral or psychological deficit as claimed. In addition, Scheffler (see cit above) teach that the classification of neuropoietic stem cells markers hinders the classification of neural precursor cells (page 353, column 1, line 10). The specification provides the cell marker expression pattern of MHP15 and MHP36 (pages 20 and 21) and that

such cells can be used to improve performance in the water maze test in rats with CA1 damage (page 24, paragraph 5). However, the specification does not provide adequate guidance indicating that the presence of these markers on a cell indicate the cells can be used in the instant invention to treat a behavioral or psychological deficit or that any pluripotent epithelial cell can function in the instant invention. The specification does not correlate the hippocampal CA1 derived neuroepithelial cells which improve water maze performance to other pluripotent neuroepithelial cells such that any pluripotent neuroepithelial cell can be used to treat any behavioral or psychological deficit. Therefore, the specification does not enable using a pluripotent neuroepithelial cells as broadly claimed to treat any animal.

The specification does not enable one of skill to conditionally immortalize cells (claim 53) because the specification does not teach how to do so and the method is not described in the art. If particular DNA sequence are required, it cannot be determined which sequences are required to conditionally immortalize the cells and what conditions provide immortality. Overall, it is unclear what characteristics conditionally immortalized cells possess.

The claims are directed toward treating any animal. Sanberg et al. (Feb. 1998, Proceedings of the 1998 Miami Biotechnology winter symposium, Vol. 38, page 139-142) teach human fetal transplantation of human pluripotent neuroepithelial cells may result in poor graft survival (page 139, paragraph 2). Sanberg et al. also teach that xenotranplanted cells are likely to be rejected without immunosuppressive agents, but such agents may preclude any therapeutic benefit because of the health risks resulting from immunosuppression (page 140, 3rd paragraph).

The specification does not correlate the transplantation of cells into rats to transplantation in humans such that a therapeutic benefit may be obtained in any animal. Thus, the specification does not provide any guidance indicating the cells obtained in the instant invention can be used in humans. Hodges et al. (1997, Pharm. Biochem. and Behavior, Vol 56, pages 763-780) teaches that it is unpredictable whether memory function can be tested in any animal with CA1 damage using the water maze test because the correlation of the extent of CA1 damage and water maze measures does not apply to all animals (page 770, paragraph bridging columns 1 and 2). The specification demonstrates transplanting neural cells to rats with CA1 damage and improving memory as determined by the water maze test (pages 22-26). Applicants suggest this invention may be used in humans or other mammals (page 2, third full paragraph). Applicants do not correlate the results obtained in rats with CA1 damage to humans or any other animal with CA1 damage in such a way that one of skill would have a reasonable expectation of success in obtaining similar results in the water maze test. The specification does not provide the parameters required to obtain similar results in any animal or an assay that could be used that can be used to test memory in any animal with CA1 damage. It would require one of skill undue experimentation to determine whether the neural cell transplantation had a therapeutic effect in any mammal without undue experimentation. Thus, the specification does not enable treating any animal as broadly claimed.

The specification does not provide adequate guidance to treat any behavioral or psychological deficit. While the specification demonstrates improving memory and spacial

learning in rats as determined by the water maze test, it is unclear that any behavioral or psychological deficit may be treated using the instant invention. For example, overeating and obesity can be associated with damage to the appetite control area of the brain. It is not clear that delivery of pluripotent neuroepithelial cells will target the appetite control area of the brain, that neuroepithelial cells can regenerate damaged tissue of the appetite control area or that regeneration of such tissue would have a therapeutic effect. The specification does not teach the type of cell or the therapeutic effective amount required to treat any behavioral or psychological deficit. Given the unpredictability in targeting the desired tissue and determining the neuroepithelial cells that can be used to graft a particular neural tissue, it is unclear how to obtain a therapeutic effect for any behavioral or psychological deficit as claimed.

Therefore, in view of the lack of guidance in the specification regarding using any pluripotent neuroepithelial cell to treat any behavioral or psychological deficit in any animal, the lack of correlation between the cells used in the invention and other pluripotent neuroepithelial cells, rats and humans, the state of the art, the examples provided and the breadth of the claims, the ordinary artisan at the time of the instant invention would not have known how to make and/or use the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 49-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "permissive conditions" (49) is indefinite. It is unclear when conditions are "permissive" or what they are permitting.

The phrase "into the damaged brain of said animal" (49) is indefinite because it does not make sense.

The phrase "mammal which comprises intracerebral transplantation" (52) is indefinite because mammals do not comprise intracerebral transplantation.

The metes and bounds of "pluripotent cells" having "neuronal and glial potential" (52) cannot be determined. The metes and bounds of neuronal or glial potential is not defined in the specification or in the art at the time of filing. As such, it is unclear whether a cell having any function of any neuronal or glial cell is encompassed by the phrase or whether the cells must have particular neuronal or glial characteristics. If so, it is unclear if such characteristics are structural or functional.

The phrase "wherein said transplanted cells migrate and differentiate to replace, or compensate for, said lost or damaged brain cells" (52) is unclear. It is unclear if the cells must migrate or differentiate or if the cells must merely replace or compensate for damaged cells. As written, the claim does not clearly set forth the function of the transplanted cells or set forth a step indicating the transplanted cells migrate or differentiate.

The phrase "conditionally immortal" (claim 53) is indefinite because the phrase is not defined in the specification and do not have an art recognized meaning. All cells are capable of being immortalized using various means known in the art. If the cells have been immortalized, the claims should clearly state they are immortal. If the phrase is intended to refer to a particular method of immortalization, the claims should clearly recite the elements required to do so.

The metes and bounds of cells from a clonal cell line (claim 55) cannot be determined. It cannot be determined if the phrase is limited to clonal cells or whether it encompasses cells derived from a clonal cell line but no longer clonal (e.g. because of mutations).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 49-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Netto (1993, Behavioral Brain Res., Vol. 58, pages 107-112).

Netto taught transplanting pluripotent, neuroepithelial cells containing CA1 cells from fetal hippocampal tissue into the hippocampus of rats submitted to VO ischemia (page 109, column 1, "grafting"; page 108, column 1, "Ischemia"; pg 107, col. line 6; page 108, para, bridging col. 1-2; para. bridging pg 109-110). The cells of Netto are "conditionally immortal"

(53) because they are capable of being immortalized. The phrase "obtainable by culturing said stem cells under permissive conditions in serum-free medium" (49) is an intended step and does not bear patentable weight because it may not occur and because it does not change the structure or function of the cell line. However, without evidence to the contrary, the cells of Netto are inherently capable of being cultured "under permissive conditions" in serum-free medium for at least a short amount of time. Culturing the cells in a growth factor, specifically FGF2, does not alter the structure or function of the cells being administered and as such does not bear patentable weight in the method claimed. Nor does claim 49 require a positive step indicating the cells are cultured in medium comprising a growth factor or FGF2. The cells inherently are "nestin-positive" because nestin is a marker of neural stem cells and the cells of Netto are neural stem cells. Therefore, Netto anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 49-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Netto (1993, Behavioral Brain Res., Vol. 58, pages 107-112) in view of Bernard (US Patent 5,580,777, 12-3-1996).

The teachings of Netto are described above. Netto did not teach making the pluripotent neuroepithelial cells clonal or immortal or culturing the cells in FGF2. However, at the time of filing, Bernard taught how to make pluripotent, neuroepithelial cells clonal and immortal and taught culturing the cells in FGF2 (col. 5, line 9, 15, 55, 64; col. 6, line 20). FGF2 is equivalent to bFGF (see specification on pg 17, line 15).

Thus, it would have been obvious to administer pluripotent, neuroepithelial cells to an animal as taught by Netto wherein the cells were immortalized, clonal and cultured in FGF2 as taught by Bernard. One of ordinary skill in the art at the time the invention was made would have been motivated to make the cells clonal and immortal to enhance survival of the cells and to increase the uniformity of the culture. One of ordinary skill in the art at the time the invention was made would have been motivated to culture the cells in FGF2 to proliferate the cells.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

6. Claims 49-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Netto (1993, Behavioral Brain Res., Vol. 58, pages 107-112) in view of Rashid-Doubell (1994, Gene Therapy, Vol. 1, Supp. 1, page S63).

The teachings of Netto are described above. Netto did not teach making the pluripotent neuroepithelial cells immortal or culturing the cells in bFGF. However, at the time of filing, Rashid-Doubell taught making a pluripotent neuroepithelial cell line immortal and culturing the

cells in FGF2 (page S63, column 1). FGF2 is equivalent to bFGF (see specification on pg 17, line 15).

Thus, it would have been obvious to administer pluripotent, neuroepithelial cells to treat an animal as taught by Netto wherein the cells were conditionally immortalized and cultured in FGF2 as taught by Rashid-Doubell. One of ordinary skill in the art at the time the invention was made would have been motivated to conditionally immortalize the cells to enhance survival and to transplant into the hippocampus (Rashid-Doubell, col. 2, last line). One of ordinary skill in the art at the time the invention was made would have been motivated to culture the cells in FGF2 to proliferate the cells.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER